# Treatment with human growth hormone in patients with Prader-Labhart-Willi syndrome reduces body fat and increases muscle mass and physical performance

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**Abstract** Twelve children with documented Prader-Labhart-Willi syndrome were treated with human growth hormone (24 U/m$^2$/week) during 1 year. The children were divided into three groups: group 1: overweight and prepubertal ($n$ = 6, age 3.8–7.0 years); group 2: underweight and prepubertal ($n$ = 3, age 0.6–4.1 years); group 3: pubertal ($n$ = 3, age 9.2–14.6 years). In group 1, height increased from −1.7 SD to −0.6 SD, while weight decreased from 1.1 SD to 0.4 SD, with a dramatic drop in weight for height from 3.8 SD to 1.2 SD. Hand length increased from −1.5 SD to −0.4 SD and foot length from −2.5 SD to −1.4 SD. Body fat, measured by dual X-ray energy absorptiometry, dropped by a third, whereas muscle mass increased by a fourth. Physical capability (Wingate test) improved considerably. The children were reported to be much more active and capable. In group 2, similar changes were seen, but weight for height increased, probably because muscle mass increase exceeded fat mass decrease. Changes in group 3 were similar as in group 1, even though far less distinct.

**Conclusion** Growth hormone treatment in Prader-Labhart-Willi syndrome led to dramatic changes: distinct increase in growth velocity, height and muscle mass, as well as an improvement in physical performance. Fat mass and weight for height decreased in the initially overweight children, and weight for height increased in underweight children.

**Key words** Body composition · Growth hormone treatment · Physical performance · Prader-Willi syndrome · Quality of life

**Abbreviations** *BMI* body mass index · *DEXA* dual X-ray energy absorptiometry · *FFM* fat free mass · *GHD* growth hormone deficiency · *hGH* human growth hormone · *LBM* lean body mass · *PWS* Prader-Labhart-Willi syndrome · *IGF* insulin-like growth factor · *WAnT* Wingate anaerobic test

## Introduction

Prader-Labhart-Willi syndrome (PWS) is caused by lack of a specific part of the paternal homologue of chromosome 15 long arm due to a deletion [14] or a maternal uniparental disomy [19, 22]. It was first described in 1956 [20] and is the most common syndromal cause of marked obesity. Its incidence is estimated at 1 in 16.000 live births [5]. The characteristic features up to infancy are

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general muscle hypotonia, feeding difficulties and underweight due to poor sucking and swallowing reflexes. Between the 2nd and 4th year of life, obesity sets in as a consequence of uncontrolled compulsive eating. Growth is characterised by moderate intra-uterine and postnatal growth delay, lack of a pubertal growth spurt and short stature as an adult. Hypogenitalism and cryptorchidism are common features in addition to delayed psychomotor development, mental retardation and behavioural problems with temper tantrums.

The link between the chromosomal disorder and the clinical manifestations is unknown. Various hypothalamic centres are assumed to be involved and several lines of evidence suggest that a growth hormone deficiency (GHD) due to hypothalamic dysregulation may contribute to an abnormal growth pattern, decreased lean body mass, muscle hypotonia, increased total body fat [16] and low energy expenditure [26].

Growth hormone (GH) response to insulin, arginine, clonidine and dopa are reported to be low-normal or blunted [1, 4, 7, 8, 16, 28], as are sleep-induced GH secretion [9] and 24-h integrated GH concentrations [1]. In contrast to simple obesity, insulin-like growth factor (IGF)-I [2, 8, 15, 16] and insulin-like growth factor binding protein-3 [16] were reported to be low or in the low-normal range.

There is some evidence that GH treatment may accelerate growth and reduce weight for height [1, 2, 15, 16, 24, 29]. Short stature, even though a distinct feature (average height of an adult PWS male is 152 cm, of a female 146 cm) [6], does not pose as much of a problem for the children with PWS and their families, as do polyphagia and overweight, poor physical and intellectual performance, and the optimal enhancement of educational and physical performance. We were therefore hoping for the fat-reducing and anabolic, muscle-increasing influence of GH to enhance strength and physical performance. We expected it to have an equally positive effect on muscle hypotonia and general adynamia and to improve well-being. The purpose of this study is to provide an accurate documentation of the GH treatment-induced changes and to support the assumed presence of a genuine GHD, secondary to a hypothalamic dysfunction. This paper presents the results of the 1st year of treatment.

## Subjects and methods

### Subjects (Table 1)

Twelve children with PWS (6 boys, 6 girls) with documented deletion or uniparental disomy of chromosome 15.

### Treatment

Administration of hGH (24 U/m$^2$/week) in daily subcutaneous injections for the duration of 1 year. No other treatment was administered, in particular no substitution of sex steroids in the older pubertal children.

### Methods

*Anthropometric measurements*

The anthropometric measurements were performed by the first author according to standard techniques [11, 21].

All auxological results are given as SDS, using the first Zurich Longitudinal Study as reference [21] with exception of arm span, hand and foot length, for which the standards of the Oosterwolde study [11] were used.

All data were processed by GAS 3.0 of the Institute for Medical Informatics, IMI, Zurich, Switzerland.

Due to the age-related variations in the syndrome's manifestations, the patients were divided into three groups:

1. Group 1: six prepubertal, obese children, aged between 3.8 and 7.0 years
2. Group 2: three young, not yet obese children, aged between 0.6 and 4.1 years
3. Group 3: three pubertal children (Tanner stage 2 and 3), aged between 9.2 and 14.6 years.

**Table 1** Study subjects

| Patient number | Sex | Age at beginning (years) | Bone age (Greulich-Pyle) at beginning (years) | Mother height (cm) | Father height (cm) | Mean target height [21] SDS |
|---|---|---|---|---|---|---|
| Group 1 | | | | | | |
| 1 | F | 3.7 | 2.5 | 167.0 | 184.0 | 0.7 |
| 2 | F | 5.0 | | 164.5 | 167.0 | −0.9 |
| 3 | F | 6.7 | 6.5 | 164.5 | 167.0 | −0.9 |
| 4 | M | 6.8 | 5.3 | 166.0 | 183.0 | 0.4 |
| 5 | F | 7.0 | 5.8 | 160.0 | 178.0 | −0.4 |
| 6 | M | 7.0 | 7.8 | 163.0 | 172.0 | −0.6 |
| Group 2 | | | | | | |
| 7 | M | 1.5 | 0.8 | 152.0 | 165.0 | −1.9 |
| 8 | M | 1.8 | 1.3 | 171.0 | 173.0 | 0.1 |
| 9 | M | 4.1 | 2.0 | 168.0 | 168.0 | −0.5 |
| Group 3 | | | | | | |
| 10 | F | 9.0 | 11.5 | 169.0 | 183.0 | 0.8 |
| 11 | M | 13.5 | 14.5 | 162.0 | 174.0 | −0.5 |
| 12 | F | 14.6 | 12.5 | 155.5 | 170.0 | −1.4 |

*Body composition*

Body composition was determined by dual-energy X-ray absorptiometry (DEXA) (Hologic QDR-2000, Waltham, Mass., USA, Software version 7.10 B).

*Anaerobic performance (ergometer)*

Muscle endurance and peak power were measured by the Wingate anaerobic test (WAnT), which is a 30-s cycling test at 'all-out' speed, against a constant braking force (Fleisch-Metabo mechanical ergometer, Switzerland, with pedal revolutions read continuously by a counter) [12]. The test was preceded by a 4-min warm up (pedalling at a mild pace, which yielded a heart rate of 110–130 beats/min), interspersed by several all-out sprinting trials of 2–3 s each. These trials were used for learning the sprinting task, as well as for determining the braking force that would subsequently be used in the test. On the command 'start', the subject started pedalling at maximal speed. Encouragement was given throughout the 30-s period. Two performance indices were calculated: peak power (the highest mechanical power at any 3-s period) and mean power (the power averaged over 30 s). These powers were calculated in Watts per kilogram body weight and as a percentage of normal values [3, 12].

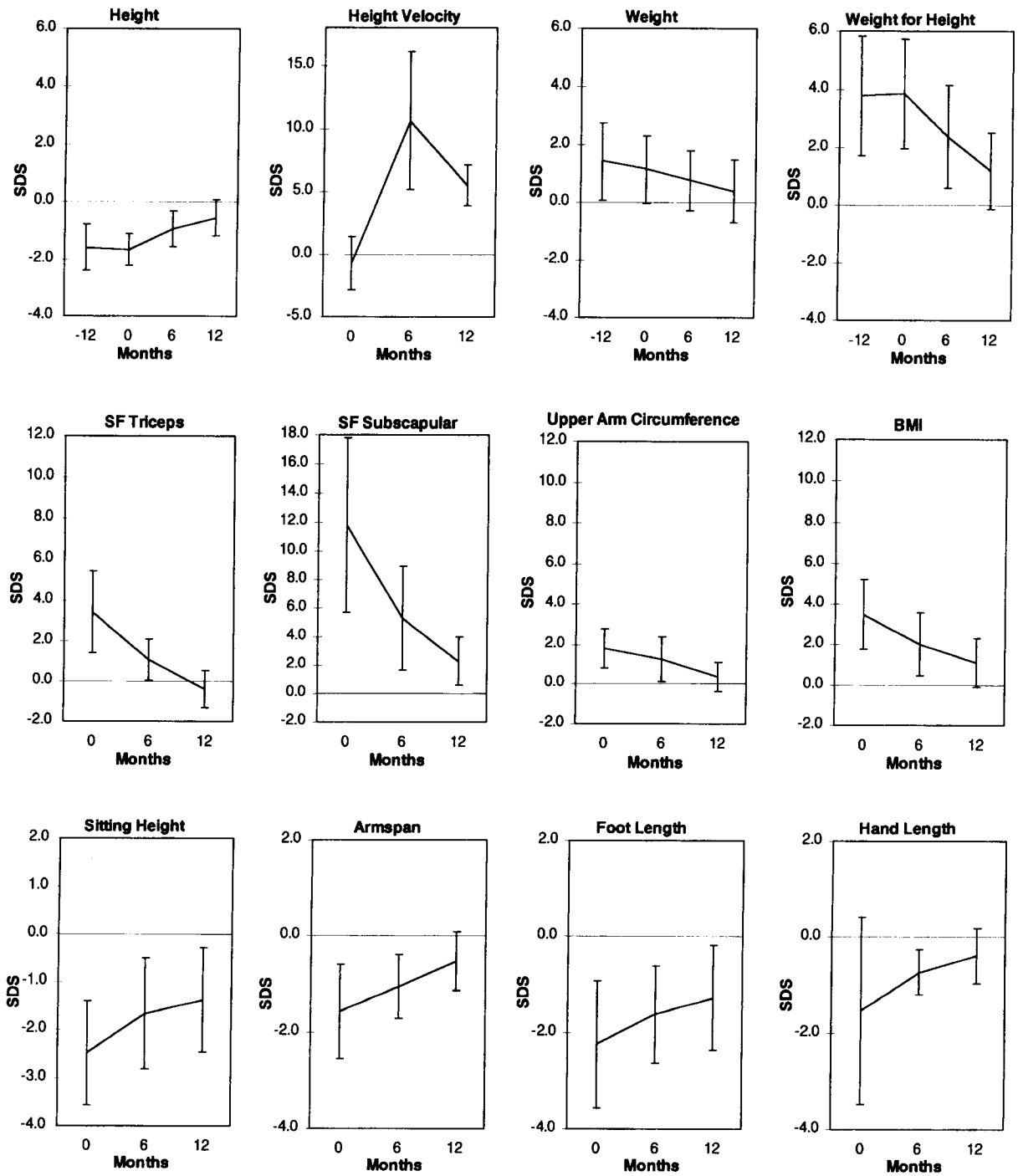


**Fig. 1** Auxology values (SDS) of group 1 (3.8–7.0 years; $n = 6$; mean ± 1 SD) during 1 year of treatment

*Physical activity pattern (parents' opinion)*

Parents' impression was obtained by means of a semistructured interview prior to the treatment, and after 6 and 12 months. This interview consisted (1) of open-ended questions on the changes to which the parents gave an answer by freely reporting what they had noticed; and (2) of specific questions relating to physical activity, namely on the differences compared to siblings and other children, on the activity itself (kind of activity, favourite activity, endurance) and differences found compared to the pre-treatment situation. For example: when parents told in the interview about their favourite family sport activity being the Sunday walk or an excursion on bicycles, they were further asked about how long and intensive this activity was and how the child behaved during this activity or whether it complained.

*Laboratory measurements*

Blood samples were taken between 8 a.m. and 9 a.m., after a 12-h overnight fast. IGF-I was measured in sera after acid ethanol extraction as described [31]. Tests of significance were performed with One Sample Wilcoxon test, a $P$ value of less than 0.05 was considered significant.

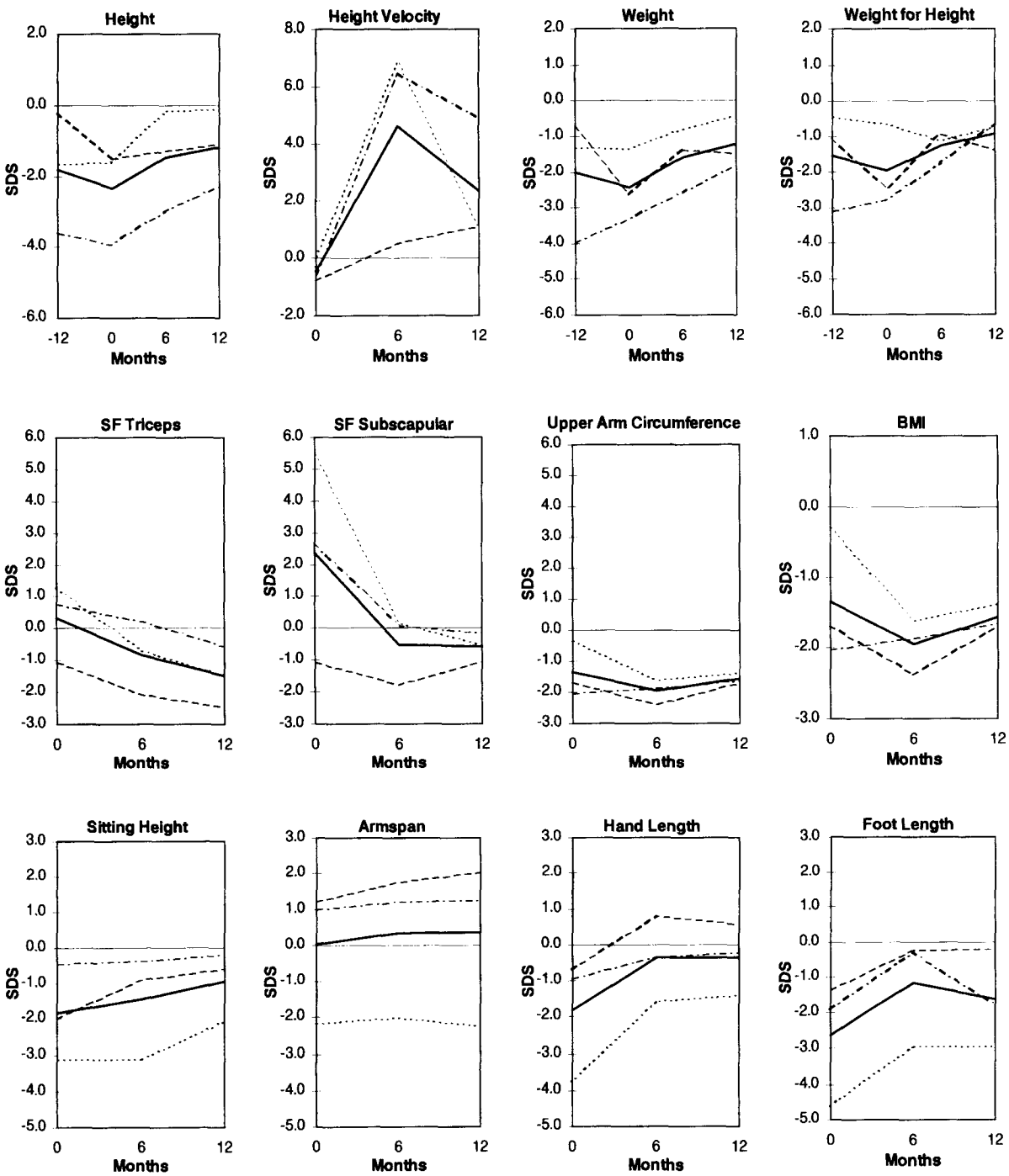


**Fig. 2** Auxology values (SDS) of group 2 (0.6–4.1 years; $n = 3$) during 1 year of treatment (——— Mean – – – patient 7 –·– patient 8 ··· patient 9)

## Results

### Anthropometriic data

*Group 1 (n = 6, age 3.8–7.0 years) (Fig. 1)*

During the 12-month treatment, height increased from −1.7 SD to −0.6 SD and growth velocity increased from −0.7 SD (6.0 cm/year) before treatment to 5.5 SD (10.8 cm/year). Weight decreased from 1.1 SD before treatment to 0.4 SD after 12 months. However, weight change in relation to the reference data only insufficiently illustrates the physical appearance in the sense of thin or fat, because growth velocity increased. Weight development in relation to height is a better approximation to the phenotype. Weight for height decreased dramatically from 3.8 SD to 1.2 SD after 12 months and body mass index (BMI) from 3.5 SD to 1.1 SD (19.7 kg/m$^2$ to 16.8 kg/m$^2$). The thickness of both

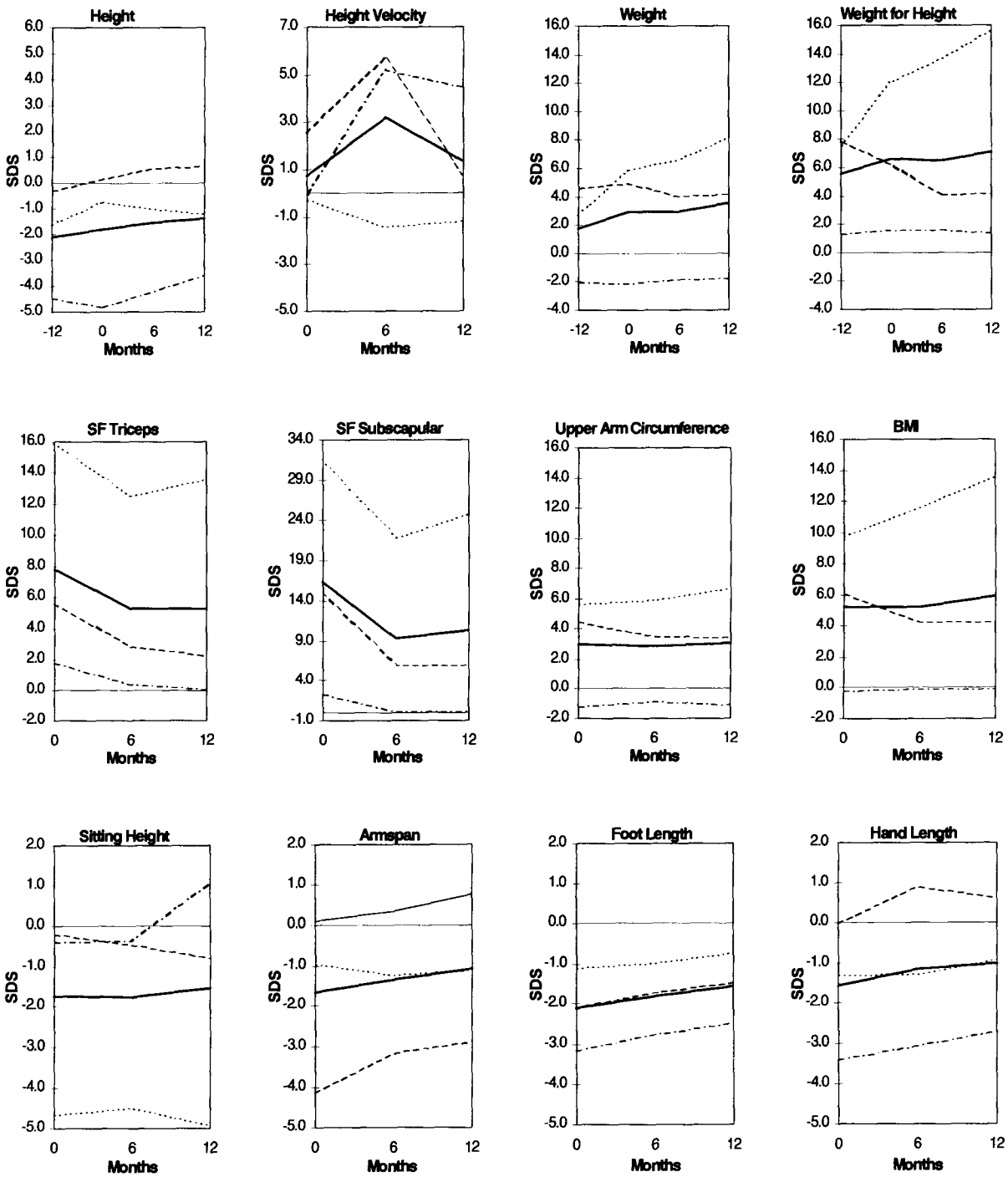


**Fig. 3** Auxology values (SDS) of Group 3 (9.2–13.8 years; $n = 3$) during one year of treatment (——— Mean – – – patient 10 –·– patient 11 ··· patient 12)

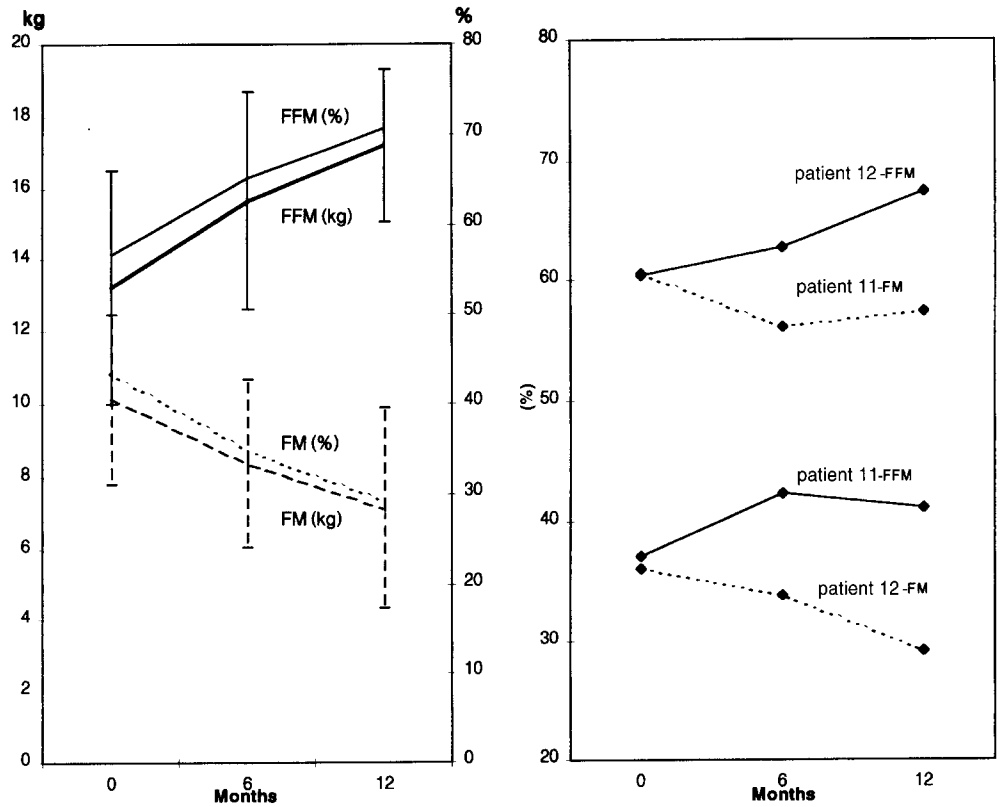


**Fig. 4A** Fat free mass and fat mass (kg,%) of group 1 ($n$ = 6; age 3.7–7.0) **B** Fat free mass and fat mass (%) of two patients of group 3 [age 14.6 (patient 12); 13.5 (patient 11)]

skinfolds decreased as treatment progressed, both over the triceps (from 3.4 SD to −0.4 SD) and subscapularly (from 11.8 SD to 2.3 SD). Arm circumference dropped from 1.8 SD to 0.4 SD. In terms of SDS difference, the increase in hand length (from −1.5 SD to −0.4 SD), foot length (from −2.2 SD to −1.3 SD), arm span (from −1.6 SD to −0.5 SD) and sitting height (from −2.5 SD to −1.4 SD) was similar to the increase in height.

*Group 2 ($n$ = 3, age 0.6 to 4.1 years) (Fig. 2)*

Height increased from −2.4 SD to −1.2 SD. But in contrast to the older children of group 1, these very young and initially underweight children showed an increase in weight for height from −2.0 SD to −0.9 SD. However, skinfolds decreased, both over the triceps (0.3 SD to −1.5 SD) and subscapularly (from 2.4 SD to −0.6 SD). The other parameters changed similarly to those of group 1.

*Group 3 ($n$ = 3, age 9.2 to 14.6 years) (Fig. 3)*

The results of group 3 reflect the small size and heterogeneity of this group, due to the major differences in height and particularly in weight and bone age. Height increased only moderately from −1.8 SD to −1.4 SD. Weight for height increased further from 6.6 SD to 7.1 SD, but even in these patients, skinfolds decreased, although to a lower extent (triceps from 7.8 SD to 5.3 SD; subscapularly from 16.3 SD to 10.3 SD) in the presence of an unchanged arm circumference (3.0 SD).

## Body composition

*Body composition measured by DEXA (Fig. 4)*

Only in older children (group 1 and 3) could body composition be determined by DEXA, due to the need for sedation in very young children. In one child of group 3, the second measurement could not be performed for technical reasons.

In group 1, fat tissue dropped from an initial 43% to 29% (from 10.2 kg to 7.3 kg) after 12 months, which corresponds to a decrease of 35%, whereas fat free mass (FFM) increased from 57% to 71% (from 13.2 kg to 16.5 kg), representing a 24% increase. In group 3, fat tissue dropped from 54% to 50% (from 33.6 kg to 38.7 kg). FFM increased from 46% to 50% (from 29.2 kg to 38.6 kg).

## Physical performance

*Anaerobic performance measured on the ergometer (Table 3)*

This test was performed with four children of group 1, all of them approx. 7 years of age at the beginning of the

treatment (age distribution 6.8–7.0 years) and with one child of group 3, since one child of group 3 was too handicapped and the other one too obese to perform this test. The other children were too short.

Table 3 shows the results of the WAnT. There was an increase in peak and mean power per kg body weight in group 1 from pre-treatment to 12 months later. The increase, whether expressed per kg body weight or as a percentage of a normal population, all showed an increase which nearly reached significance ($P = 0.08$–$P = 0.05$).

*Physical activity pattern: parents' opinion*

Parents, physiotherapists and paediatricians unanimously reported an increase in physical activity and performance. At the same time, the children became more attentive and more lively, which made them more independent, more self-assured and less anxious.

The improvement in physical performance was the most important therapy effect for the parents, even more than the loss of weight. As an example, a walk with the family of 3 h had been impossible before treatment and was now possible without the child complaining. Likewise, the children became able to climb up the wall bars or the climbing pole.

Serum concentrations of IGF-I (Fig. 5)

Before treatment, the children of our study had lower IGF-I serum concentrations when compared to those of age-matched normal-weight children (SDS: $-0.6 \pm 0.8$, $P = 0.03$) [32]. During hGH treatment, IGF-I (SDS: $2.0 \pm 1.4$) rose to the supraphysiological range in the first 6 months and remained stable thereafter.

## Discussion

GH treatment led to remarkable clinical and auxological changes in the prepubertal and initially obese children with PWS. All prepubertal children showed an impressive increase in growth velocity and a distinct catch-up growth. In terms of SDS difference, the increase in foot length, hand length and arm span was of the same order as the increase in height. One year into treatment, mean height was still below the age-related mean, but catch-up growth continued.

All prepubertal children, who were obese before treatment, showed a distinct decrease in weight for height, BMI, skinfolds thickness and body fat measured by DEXA, but after the 12-month treatment period, not all body fat parameters had dropped to the normal range and body fat was still elevated. Subscapular fat was greater than over the triceps, both before and after the 12-month treatment. Fat distribution, in PWS typi-

**Table 2** Fat free mass (FFM) measured by DEXA compared with available normal data [13]

| Patient | Group | Onset therapy | | | | 6 Months | | | | 12 Months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height | FFM (kg) real | FFM (kg) expected | Difference | Height | FFM (kg) real | FFM (kg) expected | Difference | Height | FFM (kg) real | FFM (kg) expected | Difference |
| 1 | 1 | 94.00 | 9.86 | NA | NA | 98.80 | 12.74 | NA | NA | 103.70 | 14.11 | NA | NA |
| 2 | 1 | 106.70 | 14.55 | NA | NA | 112.50 | 16.03 | NA | NA | 117.00 | 16.73 | NA | NA |
| 3 | 1 | 111.20 | 12.64 | NA | NA | 118.40 | 16.23 | 19.00 | −2.77 | 123.40 | 17.14 | 20.53 | −3.39 |
| 4 | 1 | 115.20 | 15.92 | NA | NA | 122.40 | 18.33 | 21.26 | −2.93 | 127.00 | 20.40 | 23.13 | −2.74 |
| 5 | 1 | 115.50 | 15.08 | NA | NA | 123.40 | 17.56 | 21.67 | −4.11 | 128.80 | 20.41 | 23.87 | −3.45 |
| 6 | 1 | 111.80 | 11.35 | NA | NA | 117.70 | 12.98 | 19.00 | −6.02 | 122.10 | 14.35 | 20.07 | −5.71 |
| 11 | 3 | 152.70 | 35.42 | 37.98 | −2.56 | 155.30 | 43.96 | 40.03 | 3.93 | 157.5 | 48.87 | 41.76 | 7.11 |
| 12 | 3 | 137.70 | 22.96 | 26.38 | −3.42 | 141.30 | 25.87 | 28.35 | −2.48 | 143.7 | 28.40 | 29.65 | −1.25 |
| | Mean | 118.10 | 17.22 | 32.18 | −2.99 | 141.3 | 25.87 | 28.35 | −2.40 | 127.90 | 22.55 | 26.50 | −1.57 |

**Table 3** Wingate anaerobic test

| Group ($n$) | Months | Peak power per kg | Peak power %norm | Mean power per kg | Mean power %norm |
|---|---|---|---|---|---|
| 1 ($n$ = 4) | 0 | 3.36 ± 0.63 | 57.52 ± 7.12 | 3.05 ± 0.47 | 58.9 ± 8.4 |
| | 12 | 6.42 ± 1.32 | 100.4 ± 16.1 | 4.54 ± 0.54 | 82.5 ± 9.4 |
| 3 ($n$ = 1) | 0 | 3.9 | 41 | 2.6 | 39 |
| | 12 | 5.7 | 57 | 3.9 | 57 |

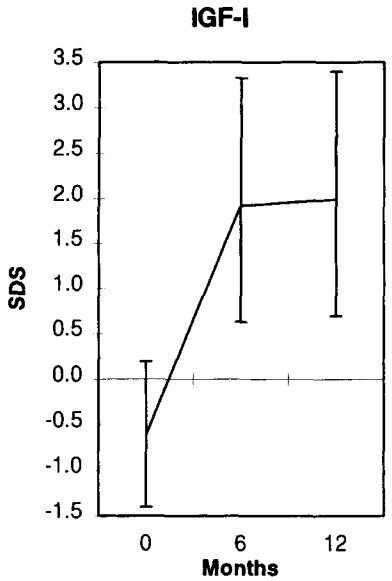


**Fig. 5** IGF-I of all subjects (0.6–13.8 years; $n$ = 12; mean ± 1 SD) during 1 year of treatment

cally concentrated on the trunk [20], is maintained even after 12 months of treatment.

Estimates based on anthropometric measurements and DEXA measurements revealed a distinct increase in lean body mass (LBM), both in relative figures (%) as well as absolutely (kg). Arm circumference dropped much less than triceps skinfolds, suggesting that the LBM increase exceeded the normal growth-related increase that one would expect.

The results of the anaerobic performance test confirmed, at least in the older prepubertal children, that the increase in muscle mass was accompanied by an improvement in physical performance. Parents reported that the children showed a higher physical activity and also much more enjoyed it, which is of particular interest. GH treatment seems to bring about not only an increase in muscle mass and physical performance, but also to cause the children to be more active, which may, additionally to the direct effects of GH, also have a positive influence by increasing energy expenditure and muscle mass and decreasing body fat.

In the very young children who were underweight at the beginning of treatment, an increase of weight for height was seen, almost exclusively due to an increase of LBM, since subcutaneous fat decreased. GH treatment in young and older children therefore seems to have the same effects with the exception of weight, probably because, in very young children, muscle mass increase outweighs body fat decrease.

The pubertal obese children showed a tendency for the same changes as the younger children, even though to a far lower extent. The small sample size and heterogeneity of the group as regards weight, height and bone age render conclusions difficult. In addition, all three patients had a non-substituted partial gonadotropin deficiency. Generally, only a moderate increase in height was observed, probably due to insufficient sex steroid levels and advanced bone age. Nevertheless the SDS increase in hand length, foot length and arm span was found to be of a similar order to the increase in body height. Weight for height rose further, but skinfolds decreased, even though to a lower extent than in the other groups.

Treatment effects in terms of height, weight, and weight for height were in agreement with earlier publications [2, 15, 16, 24, 29]. It was not possible to compare effects on growth of the extremities, changes in physical performance and physical activity, because to our knowledge, these effects have not been studied so far.

As other authors, we found some evidence in favour of a hypothalamic GHD in PWS: pre-treatment IGF-I was significantly lower than in normal-weight children, but not as low as expected in GHD. This may be explained by the fact that IGF-I is related to food intake and is increased in normal obese children [18, 30]. Moderately reduced IGF-I levels in PWS therefore constitute an argument in favour of GHD. Furthermore, increased total body fat as well as decreased absolute FFM is a typical finding in GHD [17, 25, 27]. By contrast, in simple obesity, increased total body fat is found together with increased absolute FFM [10] – which is probably due to the fact that it simply needs more muscle mass to carry around a heavy body. Therefore, we tried to compare absolute FFM measured by DEXA with normal data. So far, however, there are very few reference values for the absolute FFM in children. Lazarus et al. [13] have published standards based on age quintiles and sex. These tables contain age and the corresponding mean height. Since PWS children are below average in height, we plotted their data against height in the table, and not against the age. By interpolating height data we calculated the corresponding expected FFM in kilograms and compared it to the real absolute FFM in kg of the relevant child (see Table 2). At the beginning of the treatment, however, the children of the study were too young and too small for the reference data. Therefore, this comparison could only be

made 6 and 12 months into treatment and only in six out of nine children. Absolute FFM was found to be lower than expected after 6, but also after 12 months. The mean difference between real and expected absolute muscle mass was −2.4 kg after 6 months and −1.6 kg after 12 months. Formally, it was not possible to prove a reduced FFM before treatment due to the lack of normal values for small children, but extrapolation of 6- and 12-month data, as well as the assessment of anthropometric data may allow the conclusion that FFM was also reduced before treatment, as it is the case in GHD.

GH treatment in PWS leads to marked changes. Weight for height decreased in overweight children and increased in underweight children. Body fat decreased and an increase in growth velocity and height, as well as in growth of hands and feet was seen. With the increase in muscle tissue, physical performance improved. Parents, care personnel and physiotherapists were highly pleased about the higher physical activity and report that the children now much more enjoy physical activity.

Age-related evaluation of our data suggests that if GH treatment is taken into consideration, it should be instituted as early as possible, in any case before pubertal development sets in. In pubertal children, treatment-induced changes were poor, which may partly be attributed to the non-substitution of the partial gonadotropin deficiency. Based on further evidence of GHD in PWS and because of the supraphysiological IGF-I levels under treatment, it may be concluded that the administrated, moderately supraphysiological GH dosage was too high. Further studies with physiological substitution dosage should follow.

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